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Increased absorption of phytosterols is the simplest and most plausible explanation for coronary artery disease risk not accounted for by non-HDL cholesterol in high cholesterol absorbers

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This commentary refers to 'Intestinal cholesterol and phytosterol absorption and the risk of coronary artery disease' by J. Plat *et al.*, 2021;42:281–282.

We appreciate the interest of Plat *et al.* in our paper.[1] They argue that the coronary artery disease (CAD) risk associated with *ABCG5/8* variants that is not accounted for by non-HDL cholesterol could be explained by several other lipid-related parameters including LDL sub-fractions and oxidized LDL. We note that genome-wide association studies (GWAS) of NMR-based measures[2,3] demonstrate that *ABCG5/8* variants have similar patterns of effects on LDL and VLDL sub-fractions as many non-HDL/LDL cholesterol associated variants in other genes including *PCSK9*, *LDLR*, and *CELSR2*. Differences in sub-fraction profiles of *ABCG5/8* and other variants are therefore unlikely to account for the excess CAD risk. Also, a GWAS study on oxidized LDL levels[4] did not show association with *ABCG5/8* variants, while a

Table 1 The mean absolute levels of phytosterols per genotype group (*N* = 3039)

ABCG-[5/8]	Coding change	rsName[EA]	N per genotype (0/1/2)	Stigmasterol mean (μmol/mL)	Sitosterol mean (μmol/mL)	Campesterol mean (μmol/mL)
5	p.Phe624Leu	rs150401285[G]	3020/19/0	0.033/0.095/-	0.266/0.500/-	1.611/2.981/-
5	p.His250Tyr	rs776502883[A]	2989/50/0	0.033/0.102/-	0.263/0.580/-	1.601/2.946/-
5	p.Arg198Gln	rs141828689[T]	2985/54/0	0.033/0.045/-	0.266/0.315/-	1.612/1.910/-
5	p.Gly27Ala	rs56204478[G]	2988/51/0	0.033/0.068/-	0.265/0.383/-	1.609/2.248/-
8	p.Asp19His	rs11887534[C]	2773/259/7	0.034/0.023/0.028	0.273/0.215/0.180	1.645/1.361/1.101
8	Intronic	rs4299376[G]	1520/1276/242	0.028/0.037/0.054	0.239/0.285/0.382	1.461/1.728/2.160
8	p.Gln271Arg	rs770309304[G]	2999/40/0	0.033/0.146/-	0.263/0.834/-	1.593/5.058/-
8	p.Arg263Gln	rs137852990[A]	2967/70/2	0.032/0.093/3.879	0.264/0.420/12.650	1.599/2.566/13.333
8	p.Trp361Ter	rs137852987[A]	2980/59/0	0.033/0.065/-	0.266/0.331/-	1.609/2.116/-
8	p.Thr400Lys	rs4148217[A]	1990/926/123	0.035/0.030/0.030	0.278/0.248/0.237	1.669/1.536/1.435

The mean absolute levels (calculated on log-transformed values and transformed back to the original scale) for non-carriers/heterozygous/homozygous carriers of the effect allele (EA).

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missense variant in *APOB* associated with oxidized LDL, but not with cardiovascular events. Thus, the excess CAD risk for *ABCG5/8* variants is also unlikely driven by their association with oxidized LDL. Plat *et al.* also argue that our study lacks consideration of other essential proteins in sterol transport. However, not investigating other proteins does not invalidate our results on genetic variation in *ABCG5/8*.

While our results do not prove a causal role of phytosterols in atherosclerotic disease, we consider elevated phytosterol levels driven through the *ABCG5/8* variants the simplest and most plausible explanation for the excess CAD risk, for reasons thoroughly discussed in the manuscript. We do not agree that our conclusion and the translational perspective of our study needs revising.

Phytosterols have a log-normal distribution. In our data ($N = 3039$) (Table 1), the mean absolute stigmasterol, sitosterol, and campesterol levels were 0.033 [interquartile range (IQR) 0.020–0.066], 0.267 (IQR 0.172–0.414), and 1.618 (IQR 1.045–2.455) μg/mL, respectively (calculated on log-transformed values and transformed back to the original scale). One SD change in log-transformed phytosterol levels corresponds to 218%, 96%, and 96% change in absolute levels of stigmasterol, sitosterol, and campesterol, respectively. Thus, for example, the increasing sitosterol levels of 0.27 SD conferred by each allele of the intronic variant, corresponds to ∼26% change in absolute levels.

When our study was performed, we did not measure cholesterol and cholestanol with the phytosterols. Cholesterol absorption biomarkers such as phytosterols or cholestanol provide information about whether elevated cholesterol levels are due to hyperabsorption, as opposed to hypersynthesis. In our study, the phytosterols are used for this purpose, so data on additional absorption biomarkers are not necessary. We also point out that cholestanol data would not inform about the *ABCG5/8* associated CAD risk not explained by non-HDL cholesterol. In addition to the use of phytosterol levels as indicators of cholesterol absorption, previous studies support the atherogenic impact of these sterols themselves. The CAD risk that is not accounted for by non-HDL cholesterol for *ABCG5/8* variants, may thus 'relate to cholesterol absorption as such', through their correlation with phytosterols.

Conflict of interest: none declared.

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